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Commentary

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Drug Repurposing: Far Beyond New Targets for Old Drugs

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Abstract. Repurposing drugs requires finding novel therapeutic indications compared to the ones for which they were already approved. This is an increasingly utilized strategy for finding novel medicines, one that capitalizes on previous investments while derisking clinical activities. This approach is of interest primarily because we continue to face significant gaps in the drug–target interactions matrix and to accumulate safety and efficacy data during clinical studies. Collecting and making publicly available as much data as possible on the target profile of drugs offer opportunities for drug repurposing, but may limit the commercial applications by patent applications. Certain clinical applications may be more feasible for repurposing than others because of marked differences in side effect tolerance. Other factors that ought to be considered when assessing drug repurposing opportunities include relevance to the disease in question and the intellectual property landscape. These activities go far beyond the identification of new targets for old drugs.

KEY WORDS: drug repurposing; drug–target interactions; intellectual property; side effect tolerance; target identification.

There are two major "unknown unknown" categories in drug discovery [1] that can be linked to the main reasons for failure in drug approval, namely safety and efficacy [2]. The first category is related to the toxicological and pharmacokinetic profiles of the new molecular entity (NME), and it is mainly addressed in phases I and IIa clinical trials, following multiple preclinical evaluations: these evaluate the therapeutic regimen (i.e., dose and frequency) and safety aspects concerned to the NME. The second category relates to the protein target and biological pathway that are subject to therapeutic interference, and it is indirectly linked to the clinical efficacy of the NME under investigation: in this case, the question being addressed is whether the NME-induced perturbation of the chosen (hypothesized) target or pathway leads to the desired clinical effect [3]. The uncertainty related to the unknown unknown aspect of discovery is often mitigated by eliminating some of the "unknown" elements: either the NME is well understood, i.e., an approved drug [4], or the target/pathway is well described, i.e., already successfully manipulated therapeutically [5]. Preferably, both "unknowns" have been addressed previously, with the expectation that derisking the discovery aspect may lead to a higher success rate.

The unknown unknown strategy has been rewarding, as many blockbuster franchises have emerged following this recipe, e.g., histamine H2 antagonists, proton pump inhibitors, anticoagulant/antithrombotic therapy, or drugs to reduce hypercholesterolemia [6]. However, such drugs are the result of a long, high-cost, and high-risk optimization process, often subject to "fast followers," where first-in-class does not equate with the most financially rewarding NME [7]. In order to reduce time-to-market, as well as associated costs and risks, alternative strategies have continued to emerge. In this respect, it is currently believed (though not proven) that biologics, as opposed to small molecules, carry a lower risk in terms of toxicity and pharmacokinetic profile [8], thus regulatory approval milestones seem easier to reach. Therefore, one derisking strategy is to invest in NMEs from the biologics category. Another derisking approach is to capitalize on previous investments, for example by taking an approved drug that has already been optimized for safety and efficacy in a particular indication and obtain regulatory approval for novel therapeutic applications. This is normally being referred to as drug repurposing [9] or repositioning [4] and is the focus of this contribution.

There is a widespread tendency in academia to assume that drug repurposing is just about identifying new targets for old drugs. Several aspects ought to be considered when assessing drug repurposing opportunities, including relevance to disease,

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side effect tolerability for the new indication, and intellectual property position. All these aspects are covered in the drug repurposing flowchart proposed in Fig. 1 and contextualized in the following sections.

WHY DRUG REPURPOSING?

Several factors favor the drug repurposing strategy, both at the preclinical and clinical stage [10]. One of the typical scenarios [11] in target-directed preclinical drug discovery is to initially focus on the optimization of binding affinity for the primary target, often with the simultaneous reduction of affinity for "secondary targets" (*i.e.*, selectivity). Such efforts quite often leave aside the task of target profiling of said drug candidates for other, unrelated target classes, as well as drug pharmacokinetics and safety profiling.

For example, once the role of cyclooxygenase 2 (COX-2) in inflammation and pain was established [12], COX-2 selective agents, less active on the related enzyme cyclooxygenase 1 (COX-1), were identified [13]. This was the basis for developing celecoxib (Celebrex®), which is an order of magnitude more potent on COX-2 compared to COX-1 [14]. Its therapeutic uses include osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, pain, ankylosing spondylitis, and dysmenorrhea, as indicated on the drug label [15], and it appears to have fewer toxicity issues compared to valdecoxib (Vioxx®), another COX-2 selective compound. Vioxx was withdrawn from all markets in 2004 by Merck & Co. [16]. Celebrex continues to be marketed by Pfizer and other companies. A recent publisher's notice indicates that 21 reports, by one author, on the clinical efficacy of these drugs were fabricated [17]. Literature searches indicate that celecoxib blocks with sub-micromolar affinity the dopamine transporter [18] and MAP kinase p38 alpha [17] and is a nanomolar inhibitor of carbonic anhydrase [19]. Despite these unusual off-target activities, there are no adverse events particular to celecoxib, when compared to diclofenac, naproxen, and ibuprofen, in controlled pre-marketing clinical trials [15].

However, the lack of completeness in the knowledge of drug–target interaction profiles [20], in particular for older drugs, creates opportunities for repurposing of already-approved drugs for novel therapeutic indications through the discovery of biologically and clinically relevant affinities for new targets, which play a determinant role in those indications (Fig. 1). Novel computational methods, which can estimate the target profile of small molecules with increasing levels of recall and precision, have significantly increased the scope of target space that can be explored, thus facilitating the identification of new targets for old drugs [21–23].

The other advantage is that the NME subject to repositioning is an already-approved drug, and thus, there is no need to conduct phase I and phase IIa clinical trials. This is more likely to be the case for drugs being repurposed at similar or lower dosage compared to the maximum dose that has already been approved by regulatory agencies [24]. The large body of clinical data and experience accumulated in phase III (efficacy) and phase IV (post-marketing) trials for the drug in question offer a good understanding of its profile in terms of adverse events, long-term and chronic toxicity, as well as on- and off-label effects. In general, a large literature corpus for a particular drug is regarded as beneficial since, despite potential shortcomings, the clinical observation and monitoring required (in particular in high-risk situations) is manageable. When repurposing an older drug, it is generally anticipated that costs associated with its synthesis (including potential hazardous waste) have already been addressed, which turn the therapeutic management of the new indications economically attractive. Last, but not least, repurposing may extend the patent life (*i.e.*, market exclusivity) for successful drug franchises, a pathway that has been explored by several major pharmaceutical companies.

Overall, the lack of data completeness during the preclinical phases together with the accumulation of safety and efficacy data during the various clinical phases offers a wealth of opportunities for drug repurposing. Accordingly, collecting and making publicly available as much data as possible on the target profile of drugs would limit the possibilities of repurposing from competitors.

WHICH THERAPEUTIC AREAS?

The identification of novel targets that interact with marketed drugs is the first step in assessing the repurposing potential. A drug–target interaction is generally, though not always, considered biologically relevant if its activity is equal or better than 1 μM, that is pAct ≥6, where "pAct" is the negative logarithm of biochemical or pharmacological *in vitro* assay values (mainly, pK_i, pK_b, pK_d, pIC_{50}, or pEC_{50}). However, the therapeutic relevance of these drug–target interactions is highly dependent on the strength of the experimental evidence associating said target perturbation within the clinical context of a particular disease (Fig. 1). Several public sources provide gene–disease associations [25,26]. Access to this information allows for defining the target space relevant for all diseases within a given therapeutic area, which in turn serves as the basis for identifying targets that have been linked to multiple diseases in various therapeutic areas. For example, it is widely accepted that class A aminergic G protein-coupled receptors (GPCRs) are closely associated with diseases of the central nervous system [27]. However, members of this GPCR subclass play a role in cardiovascular diseases [28] and oncology [29] as well.

An overlooked aspect that plays a critical role in drug repurposing is the level of patient compliance with respect to side effect tolerance, which differs widely according to the therapeutic area (Fig. 1). Side effects that are acceptable in some therapeutic areas, *e.g.*, for therapeutic drugs prescribed for life-threatening conditions (such as cancer), are unacceptable in other therapeutic areas, where quality of life becomes central to patient compliance (such as central nervous system). For example, celecoxib has been repurposed [4] from osteoarthritis to familial colorectal polyps [30] and colorectal cancer [31]. The practical consequence with respect to drug repurposing is that certain clinical applications may be more feasible than others because of marked differences in side effect tolerance. Accordingly, it may be easier to repurpose a neurological drug than an anticancer drug. This statement is substantiated by a recent survey on drugs approved for new indications up to 2004 [4]. Among a list of 26 repurposed drugs, 12 were neurological drugs (46%), whereas only two were anticancer drugs (8%).

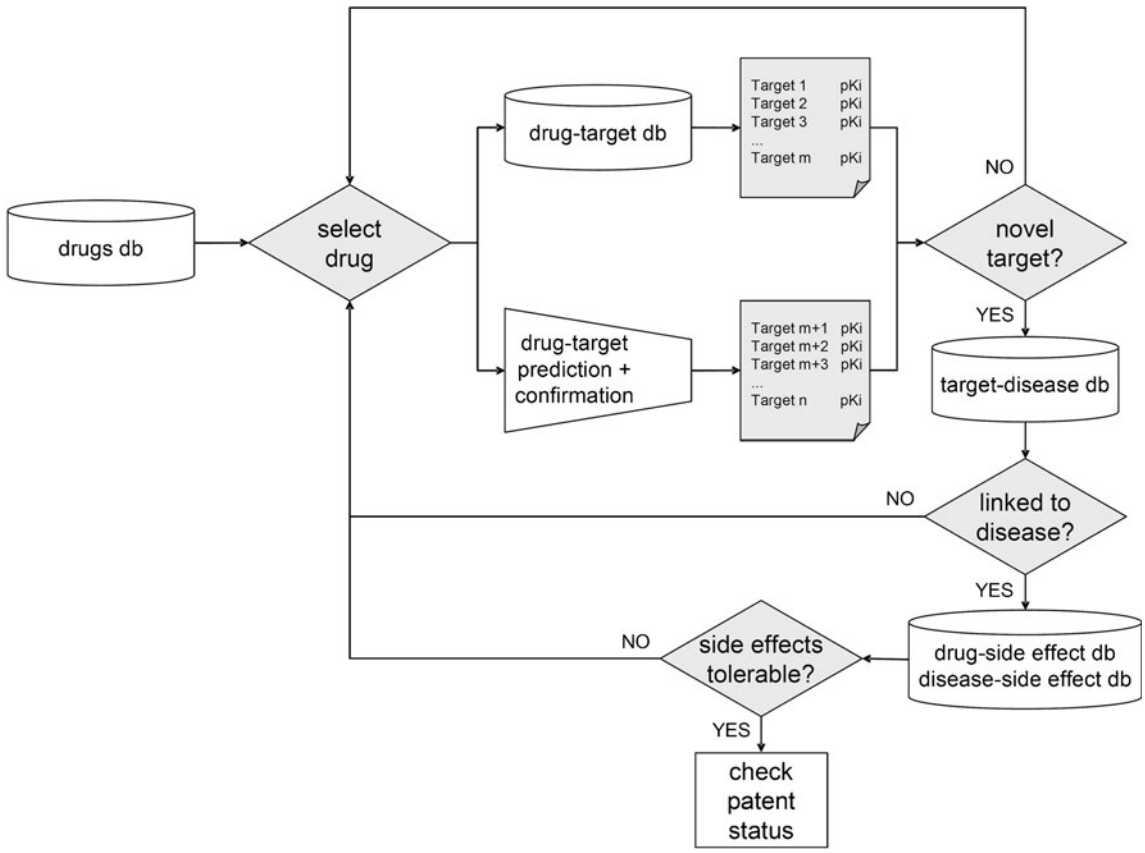

Fig. 1. Flowchart for drug repurposing beyond identifying new targets for old drugs. The abbreviation "*db*" stands for "database"

WHAT CAN BE REPURPOSED?

An intriguing aspect related to the derisking strategy involving already-approved drugs is the intellectual property landscape. Frequently, drug repurposing focuses on drugs for which patent rights on matter and/or indication have expired. This has become increasingly facilitated by the availability of commercial chemical libraries composed of out-of-patent drugs [32]. For those drugs still covered by existing patents, completely novel therapeutic applications are sought. Some may argue that composition-of-matter patents are required to gain market exclusivity. However, Celgene successfully repurposed thalidomide (Thalomid®) for leprosy, and Merz repurposed memantine for Alzheimer's disease, as Ebixa®. Thus, based on appropriate licensing, repurposing drugs that are still under intellectual property coverage is possible [33]. Another approach is to replace hydrogen with deuterium at specific positions, and several deuterated versions of approved drugs are currently undergoing clinical trials [34].

For more modern medicines that have been optimized over a length of time for a particular target (or indication), one cannot expect successful repositioning for a narrow therapeutic domain, unless selectivity is not an issue. More complex therapeutic areas, such as central nervous system linked mainly to aminergic GPCRs and oncology linked mainly to kinases, are somewhat easier to identify for approved drugs, since there is a wider array of targets and pathways that can be subjected to NME-related perturbation. Furthermore, the probability of highly similar ligands to bind two distinct targets, also referred to as cross-pharmacology, needs to be assessed for the primary target(s) of a launched drug, since different target families have been shown to have different levels of cross-pharmacology [35]. For example, GPCRs have a higher degree of cross-pharmacology among its members compared to enzymes, ligand-gated ion channels, or nuclear receptors. In addition, cross-pharmacology between some GPCRs and non-GPCR proteins has been also detected [36]. Taking into consideration the fact that some GPCRs are linked to multiple therapeutic areas (*vide supra*), drugs targeting aminergic GPCRs could constitute privileged starting points for drug repurposing. Indeed, at least 10 out of 26 repurposed drugs (38%) reviewed recently [4] have known interactions to aminergic GPCRs.

WHO'S WHO IN DRUG REPURPOSING

The outsourcing trend and the overall reduction of in-house workforce have caused a mass migration of skilled and experienced scientists from pharmaceutical industry to academia. The net effect of this trend has been an increased transfer of drug discovery know-how to academia, which effectively has shifted a large percentage of drug discovery and repurposing activities from the industrial to the academic sector. Against this backdrop, we anticipate that academia will foster most innovative efforts in drug repurposing in the immediate future. Critical to this process is the ability to pursue novel indications in the context of clinical trials. Despite the current enthusiasm, there remains an unmet critical need to fund repurposing projects into phase IIb and phase III. The burden of proof remains with the petitioner, be

it academic or industrial, which implies that any claims for clinical effectiveness against disease have to be demonstrated in clinically controlled conditions. Academic groups will have to initiate and conduct clinical trials, some of which are likely to be developed in partnership with the industrial sector. Thus, several types of repurposing models emerge: large pharmaceutical houses, major clinical enterprises, governmental facilities, and consortia involving (mostly) academic groups in partnership with industry interested in niche therapeutic areas. Recent strategic approaches and individual companies that currently engage in drug repurposing as their primary business platform have been reviewed elsewhere [37].

CONCLUSIONS

While the process of drug rescue and repurposing has receiving increased attention at the National Institutes of Health [38], this strategy is not without risks, in particular for the industrial sector. Indeed, when all pertinent factors are taken into consideration, drug repurposing may ultimately incur high costs, which may reduce even further the already diminishing resources of the pharmaceutical industry. On one hand, drugs are typically the result of a long optimization process directed to improve the affinity and selectivity (among other aspects) for a given primary target. Thus, the potency values for novel targets identified for old drugs will likely be lower than the potency for the primary target. As a consequence, one should conduct repurposing efforts for a target/indication that was not deliberately counter-selected during the initial project. If other drugs are already approved for that indication, demonstrating superiority with respect to efficacy and safety (phases III and IV) may be an insurmountable challenge [39]. According to a recent reproducibility analysis of 67 target validation studies, target–disease associations are not always fully reliable [40]. Therefore, the risks of having a second-in-class drug with lower potency that is not unambiguously linked to a certain indication should be appropriately balanced.

On the other hand, one ought to consider that the specificity (in a statistical sense) of current approaches to suggest drugs for repurposing is relatively low. Recent academic enthusiasm in this field has resulted in the publication of relatively long lists of drugs that could potentially be repurposed for a variety of indications, including tuberculosis [41], breast and prostate cancer, and myelogenous leukemia [42]. This academic trend has two (unfortunate) consequences. As this information is now public domain, even if experimentally confirmed, it still constitutes "prior art." This effectively blocks intellectual property protection and future investment in that particular combination of drugs and targets or clinical indications. Equally important, it lowers the credibility of computational approaches to drug repurposing, since it is not likely that many of these suggestions can lead to regulatory approval, which remains the only milestone for successful drug repurposing. It seems unrealistic to follow-up on all the candidates being claimed for repurposing. Rather, substantiating the relevance of all potential repurposing drugs for a given indication is likely to be a long and costly process. Taking into consideration all aspects highlighted above, the ideal candidate for a repurposing initiative would be an off-patent safe drug for which a novel target has been identified, with affinity within the maximum recommended therapeutic dose for an already-approved indication, and linked with strong supporting evidence to a therapeutically unmet need or rare disease.

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